binds a surface antigen, induces internalization and allows the immunogenic peptide to be presented by both MHC Class I and II molecules on the target cell surface to modulate immune responses. Applicants respectfully traverse this rejection. As amended in the Response and Amendment dated May 3, 2000, Claim 1 and Claims 5 to 11, 13 and 20 to 23, depending from Claim 1, require a translocation portion. For a proper 35 U.S.C. § 102(b) rejection, every element in a claim must be taught by the reference. Applicants respectfully point out that the '323 patent does not teach or suggest a translocation portion. Examiner suggests that the '323 patent's immunoglobulin molecule includes a translocation portion based on the immunoglobulin's binding and internalization. Applicants respectfully point out that internalization as taught by the '323 patent is typically considered a property of the target cell or the target cell surface component to which the immunoglobulin binds. The '323 patent does not teach or suggest an active translocation portion in the immunoglobulin as taught by the present application.

Further, Examiner points to DeFranco (1999) as evidence that antigens are taken up by B-cell receptors and on the cell surface and cycled to "internal membrane compartments." At the outset, Applicants remind Examiner that DeFranco (1999) represents the state of the art as of 1999. Applicants' priority date is May 13, 1994. Therefore, DeFranco (1999) cannot be applied as prior art against Applicants' invention. Regardless, Applicants respectfully point out that, contrary to Examiner's contention, Defranco (1999) in column 1, paragraph 3 specifically states that, once internalized, the fate of the BCR complexes is governed by whether or not the BCR complexes are bound, for example to tetanus toxoid. Defranco (1999) does not teach or suggest an immunoglobulin having an active translocation portion.

Therefore, the '323 patent does not provide a proper basis for rejection under 35 U.S.C. § 102(b).

Accordingly, Applicants respectfully request that the rejection of Claims 1, 5 to 11, 13 and 20 to 23 under 35 U.S.C. § 102(b) be withdrawn.

Examiner rejects Claims 1 to 3, 5 to 12, and 14 to 23 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification so as to enable one skilled in the art to practice the invention without undue experimentation. Applicants respectfully traverse this rejection. At the outset, Applicants remind Examiner that the level of ordinary skill in the immunological arts is very high and the technology is well developed. Examiner contends that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to "modulating the immune response." Further, Examiner argues that the specification fails to provide sufficient guidance regarding specific disorders and that Examples 1 and 2 provide "only" *in vitro* ^{51}Cr assay data that is of little relevance to *in vivo* modulation of the immune system. Again, Examiner relies on Derner (1994) and Kahan (1992) to support his contention that manipulation or modulation of *in vivo* immune responses is complex, unpredictable and outside the realm of routine experimentation. Applicants respectfully disagree. Again, Applicants point out that Derner (1994) and Kahan (1992) are inapposite because the articles relate to limitations of cell lines and immune assays in applications where the overall effects observed are not always the same as those which occur *in vivo* and where the molecular mechanisms may not reflect what happens *in vivo*. To the contrary, Applicant's *in vitro* testing precisely mimics the mechanisms *in vivo*. It is widely accepted that for any form of vaccine comprising a non-repetitive polypeptide vaccine, including T-cell dependent, the presentation of immunogenic peptides by MHC molecules is required to produce an effect *in vivo*. Examples 1 and 2 demonstrate the presentation of these immunogenic peptides by MHC molecules *in vitro*. This presentation is a necessary prerequisite for modulating the immune system response and therefore, provides a simple and acceptable correlation between the *in vitro* examples and what occurs *in vivo*. Further, Examples 1 and 2 use entirely different chimeric polypeptides to illustrate divergent applications of the present invention by demonstrating a similar effect on two different cell lines. Given the biologically distinct nature of these two chimeric polypeptides that share the three

domains taught by the present application, one skilled in the art would understand that other chimeric molecules made with this three domain design would achieve similar effects on a particular target cell.

Further, Examiner contends that demonstrating MHC presentation is not sufficient for enablement. Examiner states that MHC presentation is only component of a multi-step process leading to an immune response. Examiner argues that Applicants have not explained why the disclosed T-cell and APC clones used in the assays provide sufficient guidance to enable the claimed embodiments. While Applicants agree that an effective immune response is a multi-step process, those skilled in the art understand that T-cell dependant responses are far more prevalent than T-cell independent responses to repeat antigens. Further, those skilled in the art understand that T-cell dependant immune responses have a necessary step of MHC peptide binding events. It is understood that MHC-peptide binding events are a critical step in the immune response pathway without which no sustained immune responses, aside from T-cell independent antigens, is conferred. The chimeric molecules of the present invention produce MHC-peptide binding events. The MHC-peptide binding events are detected indirectly through CTL responses. The controls used in Examples 1 and 2 point clearly to the effects of the specific peptides within the effector portion of the chimeric molecules whereby the effect is lost to background levels without the appropriate peptide. As MHC-peptide may be used to modulate T-cell responses either through inducing cytotoxic events or through inducing helper T-cell responses and/or any other MHC-peptide-related responses, those skilled in the art will understand upon review of the present application that many strategies are possible to treat conditions requiring immunostimulation or immunosuppression. For example, the specification refers to delivering peptides *ex vivo* for induction of CTLs prior to adoptive immunotherapy (e.g. cancer) and to enhancing the T-cell activating, blocking or abrogating ability of cells already presenting the specific peptide(s) (e.g. autoimmune or inflammatory cells). Thus,

one skilled in the art is enabled to practice the full scope of the claimed invention upon review of the specification without undue experimentation.

Therefore, a rejection of Claims 1, 5 to 11, 13 and 20 to 23 under 35 U.S.C. § 112, first paragraph, as not enabled is improper.

Accordingly, Applicants respectfully request that the rejection of Claim 20 to 23 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Examiner rejects Claims 1 to 3, 5 to 12, and 14 to 23 under 35 U.S.C. § 103(a) as obvious over Casten et al. (1988) in view of Fawell et al (1994) and Noguchi et al (1994). Applicants respectfully traverse this rejection. Examiner contends that Casten et al. teaches a chimeric polypeptide comprising a binding portion having at least a portion of an immunoglobulin molecule with a specific binding affinity for a eukaryotic target cell surface component and an effector portion consisting of at least one copy of an immunogenic peptide whereby binding of the polypeptide induces internalization to allow presentation of the effector by the MHC of the target cell. Examiner acknowledges that Casten et al. does not teach the use of an HIV tat translocation portion nor does it teach a p53 effector portion. In addition, Examiner contends that Fawell et al teaches the use of the HIV tat protein for cellular translocation and that Noguchi et al teaches the use of p53 as a candidate for T-cell recognition. As Examiner knows, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive to support the combination. Nowhere in the disclosures of Casten et al., Fawell et al., and Noguchi et al. is it taught or suggested to combine a chimeric polypeptide comprising a binding portion comprising at least a portion of an immunoglobulin molecule having specific binding affinity for a eucaryotic target cell surface component; an effector portion consisting of at least one copy of an immunogenic peptide; and a signal directing the immunogenic peptide to a particular cellular compartment.

Applicants submit that, like the '323 patent, Casten et al. teaches an immunobglobulin complexed with an antigen. Casten et al. does not teach the

active internalization of the chimeric polypeptide. To the contrary, Casten et al. teaches away from internalization and processing, stating that "presentation does not require internalization or processing of the peptide antibody conjugate." (pages 176 to 177). Thus, the mode of presentation for the chimeric polypeptide in Casten et al. is on the cells' surface without requiring internalization.

Further, references such as Casten et al. and the '323 patent are indicative of the state of the art before the present invention. They teach cell surface binding or internalization through binding to a specific cell surface molecule was adequate for production of an immune response. Thus, they effectively teach away from Applicants' invention.

Examiner contends that Fawell et al. teaches the use of the HIV tat protein to confer cellular translocation on four disparate proteins. Examiner further contends that Fawell et al. teaches that HIV tat can be used as a "generic" translocation signal to "efficiently deliver heterologous molecules into cells" (page 664, paragraph 3). Thus, Examiner concludes Fawell et al. provides motivation for HIV tat's use as the translocation component in the present invention. Applicants respectfully disagree. Fawell et al. teaches the cellular delivery of "cargo" proteins. The HIV tat protein provides non-specific cell binding and translocation activities. Unlike Fawell et al., the HIV tat protein does not act as a cell binding entity. In fact, Fawell et al. teaches away from the present invention by stating that the HIV tat protein's delivery independent of cell type is a desired characteristic (see pages 664 and 668).

Examiner contends that Noguchi et al. teach the use of p53 as an "obvious candidate for T-cell recognition" because the gene is frequently mutated in tumors of experimental animal and humans" (page 3171, second paragraph, and pages 3173 to 3174). Examiner does not provide any indication that Noguchi et al. provides any motivation to combine the elements of Applicants' invention.

Therefore, for the reasons discussed above, neither Casten et al., Fawell et al. nor Noguchi et al. teaches or suggests the combination of Applicants' invention. Without any teaching or suggestion for their combination, the rejection

under 35 U.S.C. § 103(a) as obvious over Casten et al. in view of Fawell et al. and Noguchi et al. is improper.

Accordingly, Applicants respectfully request that the rejection of Claims 1 to 3, 5 to 12, and 14 to 23 under 35 U.S.C. § 103(a) be withdrawn.

In view of Applicants' remarks, the claims are believed to be in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested.

If any additional fees are due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-1265. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

Date: 9/13/00

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CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment consisting of seven (7) pages, and an Associate Power of Attorney for the application Serial No. 08/737,457 of inventors, DONALD L. N. CARDY, ET AL., filed March 12, 1997, for "IMPROVEMENTS IN OR RELATING TO PEPTIDE DELIVERY" was deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Box Non-Fee Amendment (PATS), Assistant Commissioner for Patents, Washington, D.C. 20231, on Wednesday, September 13, 2000.

Anna Lemke

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On Behalf of Kevin W. Cyr